THE USE OF DOBUTAMINE IN MYOCARDIAL INFARCTION FOR REVERSAL OF THE CARDIODEPRESSIVE EFFECT OF METOPROLOL

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- 1 Ten patients with acute myocardial infarction were infused dobutamine in increasing doses up to $15 \mu\text{g kg}^{-1} \text{min}^{-1}$.
- 2 Metoprolol (total dose 15 mg) was then given intravenously to nine of these patients and the β -adrenoceptor agonist effects produced by dobutamine were effectively reversed.
- 3 Nine patients with acute myocardial infarction pretreated with metoprolol (15 mg) were infused dobutamine $15 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 10 min. This resulted in effective reversal of the β -adrenoceptor antagonist effects induced by metoprolol, without the occurrence of serious arrhythmias or other unwanted effects.
- 4 Dobutamine may be valuable in counteracting any undesirable cardiodepressive effects of β -adrenergic receptor blocking drugs (especially the cardioselective agents) in patients with acute myocardial infarction.

Introduction

Dobutamine is a new sympathetic cardiac stimulatory drug (Tuttle & Mills, 1975) which, in the intact animal, has been shown to increase contractility and coronary flow, whilst having little effect on rate, preload or afterload (Vatner, McRitchie & Braundwald, 1974; Hinds & Hawthorne, 1975). Similar effects have been obtained in patients with chronic heart failure (Beregovich, Bianchi, Angelo, Diaz & Rubler, 1975). In experimental myocardial infarction in dogs, dobutamine in contrast to isoproterenol, increased the oxygen content of coronary sinus blood and did not increase the infarct size (Tuttle, Pollock, Todd & Trust, 1973). It should therefore be beneficial in patients with acute myocardial infarction and impaired contractility. Since β -adrenoceptor blockade is widely used in cardiovascular disease and there is a growing interest in the use of β -adrenoceptor blockade for reduction of myocardial ischemia (Waagstein, Hjalmarson & Wasir, 1974; Mueller *et al.*, 1974; Waagstein & Hjalmarson, 1975a, b), patients arriving in coronary care units will frequently be under such medication. As cardioselective β -adrenoceptor blockade seems to be the most suitable treatment in acute myocardial infarction (Jewitt & Singh, 1974), any excessive drop in cardiac output so induced should logically be prevented by treatment with a cardio-selective sympathetic stimulant in doses which could be readily adjusted to the need of the subject.

The aim of the present study was to investigate the

haemodynamic effects of dobutamine in patients with acute myocardial infarction, and to determine whether this drug can counteract the β -adrenoceptor blocking activity of metoprolol.

Methods

Nineteen patients with acute myocardial infarction were studied 2–13 days after onset of chest pain (Tables 1 and 2). Two patients had signs of left ventricular failure during the first two days after onset of symptoms but were compensated at the time of investigation. The remaining 17 patients showed no signs of failure at any time during the infarction.

Ten patients were given dobutamine as a continuous infusion using a Braun Melsungen infusion pump type 711. The rate of infusion started at $2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ and was increased every 10 min by $2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ up to $15 \mu\text{g kg}^{-1} \text{min}^{-1}$. Heart rate was calculated from the ECG during the last minute of each infusion rate. After 10 min at the maximum rate of dobutamine infusion the cardioselective β -adrenoceptor blocker, metoprolol, was injected intravenously in three doses of 5 mg at 5 min intervals in nine of the ten cases. In four cases infusion of dobutamine was stopped after the last dose of metoprolol; infusion was continued for another 15 min in five cases. Heart rate and blood pressure were monitored until steady. Blood pressure was measured

indirectly every minute with an ultrasound sphygmomanometer (Arteriosonde 1217, Roche Medical Electronic Division, Cranbury, U.S.A.), which has been shown to correlate well with invasively measured blood pressure (Hochberg & Solomon, 1971). Since blood pressure and heart rate were practically stabilized after 5 min of infusion, mean values are reported for the last 5 min of each infusion period. Pre-ejection period (PEP) was calculated from ECG lead II, phonocardiogram and carotid pulse tracing as described elsewhere (Waagstein *et al.*, 1974). $PEPI = PEP + 0.4 \times \text{heart rate}$ (Weissler, Kamen, Bornstein, Schoenfield & Cohen, 1965). The ECG was monitored for arrhythmias during the last 10 min before dobutamine infusion and during 10 min periods of dobutamine infusion at 5, 10 and $15 \mu\text{g kg}^{-1} \text{min}^{-1}$.

The effects of pretreatment with metoprolol were studied in nine patients who had (1) no treatment with β -adrenoceptor blockers within the last 24 h, (2) no clinical signs of left ventricular heart failure, (3) systolic blood pressure above 100 mm Hg, (4) no signs of bad peripheral circulation, (5) heart rate more than 50 beats/min, and (6) no AV-block I, II, or III. Those under chronic treatment with digitalis and/or diuretics were accepted. After a control period metoprolol was given intravenously in three doses of 5 mg at 5 min intervals. Five minutes after the last dose of metoprolol, dobutamine $15 \mu\text{g kg}^{-1} \text{min}^{-1}$ was infused for 10 min. After the infusion monitoring continued until heart rate and blood pressure were steady. Heart rate, blood pressure, and PEP were

measured before metoprolol, immediately before starting dobutamine infusion, shortly before the end of infusion and when a steady state was achieved after the infusion. Stroke volume was evaluated using an impedance cardiograph (Instrumentation for Medicine model 304A), which has been found to correlate well with the Fick method (Naggar, Dobnik, Flessas, Kripke & Ryan, 1975). The specification for the equipment is described elsewhere (Hill & Thompson, 1975a). Electrode tapes (Medical Product Division Minnesota Mining Manufacturing Company) were placed around the base of the neck, 3–5 cm above, around the thorax at the level of the xiphisternum and around the abdomen at least 3 cm lower. The stroke volume (SV) was calculated from the formula:

$$SV (\text{ml}) = \text{Blood resistance (ohm cm)} \times$$

$$\frac{dz/dt \times L^2 \times LVET}{(Z_0)^2}$$

Blood resistance is set to 135 for a normal haematocrit of 43.5% (Hill & Thompson, 1975a, b); dz/dt is the first derivative of change in thoracic impedance in ohm/sec; L is the mean distance between the two inner electrodes in cm; $LVET$ is ejection time in sec measured from carotid pulse tracing; Z_0 is the mean impedance in ohm. Graphical records of dz/dt and carotid pulse were obtained during midexpiratory apnoea. Values were calculated from ten consecutive beats.

Table 1 Mean and range age, laboratory data, body temperature and X-ray findings in patients treated with dobutamine infusion

n	Age (years)	SGOT _{max} (U)	SGPT _{max} (U)	SR _{max} (U)	Temp _{max} (°C)	Heart size (ml/m ²)
10	54 (32–73)	103 (34–263)	29 (12–66)	65 (30–115)	38.1 (37.2–39.7)	478 (340–620)

Normal values: GOT and GPT ≤ 17 U; heart size ≤ 450 ml/body surface area m².

Table 2 Mean and range age, laboratory data, body temperature and X-ray findings in patients treated with metoprolol and dobutamine

n	Age (years)	SGOT _{max} (U)	SGPT _{max} (U)		Temp _{max} (°C)	Heart size (ml/m ²)
9	65 (54–78)	68 (20–105)	17 (6–67)	46 (10–99)	38.3 (37.5–39.2)	450 (380–690)

Normal values as in Table 1.

Figure 1 Changes in pulse pressure in ten patients with acute myocardial infarction during infusion of dobutamine. Mean values are connected with a dotted line.

Figure 2 Changes in heart rate in ten patients with acute myocardial infarction during infusion of dobutamine. The dotted line connects mean values.

Results

Effects of dobutamine in acute myocardial infarction

Table 3 shows that intravenous dobutamine in a dose of $2.5\text{--}15\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ increased systolic blood pressure, pulse pressure, and heart rate, and decreased PEP and PEPI. Changes in pulse pressure, heart rate and PEPI for individual subjects can be seen in Figures 1, 2 and 3. The changes were seen within a few minutes in most patients and a stable response to dobutamine at each dose level was obtained within 10 min. The infusion of $2.5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ gave a significant increase in pulse pressure and a reduction in PEP and PEPI without any changes in heart rate. The infusion of $5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ resulted in a very small increase in heart rate although the pulse pressure was increased further and PEP and PEPI were

markedly reduced. The increase in pulse pressure was due to a small increase in systolic blood pressure and a small decrease in diastolic blood pressure. Increasing the infusion between $5\text{ and }15\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ resulted in a further increase in pulse pressure and decrease in PEP and PEPI but there was now a clear increase in heart rate (Table 3). There were marked variations in the response to dobutamine between the ten patients. In three patients the changes in pulse pressure and PEPI were very small. In another two there was a reduction in heart rate after infusion of dobutamine except for the infusion of $15\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$.

When metoprolol was given to five of the patients during continuous infusion of dobutamine $15\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ there was a fall in heart rate within 1 min and after 5 min the heart rate (mean $\pm$ s.e. mean) had decreased from the maximum level 112 ± 9.4 to 74 ± 4.8 beats/min ($P < 0.02$), which matched the

Table 3 Mean $\pm$ s.e. mean haemodynamic parameters in ten patients with acute myocardial infarction before and during continuous infusion of dobutamine increased in steps from 2.5 to $15\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$.

	Dobutamine infusion ($\mu\text{g kg}^{-1}\text{ min}$)						
	Control	2.5	5	7.5	10	12.5	15
Heart rate (beats/min)	78 ± 4.6	80 ± 5.9	85 ± 6.3	93 ± 7.7	98 ± 7.6	103 ± 7.8	107 ± 7.9
Systolic BP (mm Hg)	117 ± 5.4	120 ± 4.1	125 ± 4.7	127 ± 4.7	131 ± 5.2	136 ± 6.1	139 ± 6.3
Diastolic BP (mm Hg)	78 ± 2.0	75 ± 2.4	73 ± 2.8	73 ± 3.1	74 ± 3.5	75 ± 3.9	76 ± 4.0
Pulse pressure (mm Hg)	39 ± 4.7	45 ± 5.0	49 ± 5.5	54 ± 5.9	57 ± 6.4	61 ± 7.1	62 ± 7.1
PEP (ms)	108 ± 6.1	99 ± 6.7	92 ± 6.5	89 ± 6.9	86 ± 6.7	82 ± 6.5	80 ± 6.4
PEPI (ms)	139 ± 4.4	128 ± 5.6	125 ± 5.6	123 ± 6.4	122 ± 6.2	120 ± 6.2	119 ± 6.0

Figure 3 Changes in pre-ejection period index (PEPI) in ten patients with acute myocardial infarction during infusion of dobutamine. Mean values are connected with a dotted line.

Figure 4 Changes of stroke volume and cardiac output in nine patients with acute myocardial infarction after metoprolol and dobutamine.

control value of 76 ± 7.4 beats/min. After stopping dobutamine infusion there was a further decrease in heart rate to 68 ± 4.0 beats/min.

Side-effects of dobutamine

Most patients experienced palpitations after infusion of $15 \mu\text{g}$ dobutamine $\text{kg}^{-1} \text{min}^{-1}$, but none complained of oppression or chest pain. Four patients desired to urinate during the infusion for 10 min of $15 \mu\text{g} \text{kg}^{-1} \text{min}^{-1}$, but this ceased when the infusion stopped. In seven of the patients there were no arrhythmias during the whole experiment. One patient had four supra-

ventricular ectopic beats (SVEB) during 10 min of the control period, and there were sixteen nodal escape beats during the 10 min period of infusion at $15 \mu\text{g} \text{kg}^{-1} \text{min}^{-1}$. Another had three monofocal ventricular ectopic beats (MVEB) during 10 min of the control period, six MVEB during 10 min of infusion of $5 \mu\text{g} \text{kg}^{-1} \text{min}^{-1}$, thirteen MVEB during 10 min of the infusion of $10 \mu\text{g} \text{kg}^{-1} \text{min}^{-1}$ and seventeen MVEB in 10 min after $15 \mu\text{g} \text{kg}^{-1} \text{min}^{-1}$. A third patient had fourteen SVEB during 10 min of control period, five SVEB during the infusion of $5 \mu\text{g} \text{kg}^{-1} \text{min}^{-1}$, but no SVEB at the higher dose levels of dobutamine. Thus, arrhythmias may have been induced by dobutamine in

Table 4 Mean $\pm$ s.e. mean haemodynamic parameters in nine patients with acute myocardial infarction before and after metoprolol (15 mg i.v.) and dobutamine (infusion rate $15 \mu\text{g} \text{kg}^{-1} \text{min}^{-1}$)

	Control	P<	Metoprolol	P<	Metoprolol + dobutamine	P<	After dobutamine withdrawal
Heart rate (beats/min)	83 ± 3.6	0.001	69 ± 3.1	0.005	77 ± 2.8	0.005	72 ± 2.8
Systolic BP (mm Hg)	132 ± 4.1	0.02	124 ± 5.8	NS	126 ± 6.8	0.05	117 ± 7.2
Diastolic BP (mm Hg)	82 ± 3.9	NS	80 ± 4.0	NS	78 ± 3.8	NS	77 ± 4.3
PEP (ms)	97 ± 3.1	0.001	108 ± 3.6	0.02	94 ± 4.1	0.005	108 ± 3.2
PEPI (ms)	130 ± 3.1	0.025	136 ± 4.2	0.02	124 ± 4.3	0.01	137 ± 3.6
Stroke volume (ml)	65.9 ± 4.6	0.05	73.8 ± 4.9	NS	77.0 ± 6.7	NS	68.3 ± 4.5
Cardiac output (l min^{-1})	5.5 ± 0.4	NS	5.1 ± 0.3	0.025	5.9 ± 0.5	0.01	4.9 ± 0.3

two of the patients, but in no case were the arrhythmias serious or frequent. There were no other complaints from the patients during the infusion of dobutamine.

Effect of metoprolol and dobutamine in acute myocardial infarction

Table 4 shows that the cardioselective β -adrenoceptor blocker metoprolol, in a dose of 15 mg intravenously, reduced heart rate and systolic blood pressure, and increased both PEPI and stroke volume. The cardiac output and the diastolic blood pressure were not significantly changed after metoprolol except in one case who initially had a high cardiac output attributed to enhanced sympathetic activity. He showed a marked fall in cardiac output due to reduction in heart rate and stroke volume. Ten minutes after the injection of metoprolol the infusion of dobutamine $15 \mu\text{g kg}^{-1} \text{min}^{-1}$ was started and produced a maximal effect on the various parameters after 10 min. Figure 4 illustrates individual changes in stroke volume and cardiac output in nine patients receiving metoprolol and dobutamine. There was usually a significant increase in heart rate and cardiac output while PEPI was reduced to control value and diastolic pressure was not changed. The stroke volume increased in three patients, fell in one (who was in left ventricular failure) and remained unchanged in five. The cardiac output increased in all but one. Ten minutes after stopping dobutamine infusion all parameters had returned to the level recorded after metoprolol alone, and remained unchanged for another 15 min at least, indicating effective β -adrenoceptor blockade.

Side-effects from metoprolol and dobutamine

In three of the ten cases SVEB and VEB were seen during the study but were not clearly related to the treatment. None of the patients had chest pain, but most experienced palpitations. However, none of the patients experienced palpitations when dobutamine was given under β -adrenoceptor blockade. Dyspnoea was not experienced and there were no lung râles or any unwanted reduction in blood pressure or heart rate in the combined metoprolol and dobutamine study.

Discussion

None of the patients in the present study was in urgent need of inotropic support. However, among patients with no signs of cardiogenic shock or overt left ventricular decompensation the individual response to dobutamine varied. In most cases, dobutamine in doses up to $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ increased pulse pressure and shortened the pre-ejection period as well as the

rate adjusted pre-ejection period with very little effect on diastolic pressure and heart rate. With higher doses of dobutamine, pulse pressure increased and PEP and PEPI decreased further, but there was also a significant increase in heart rate. Changes in these parameters were influenced by existing autonomic activity, heart function and peripheral vascular resistance. An increase in pulse pressure with little or no decrease in diastolic blood pressure is interpreted as an increase in stroke volume (Jewitt, Birkhead, Mitchell & Dollery, 1974). The shortening of PEP and PEPI is interpreted as an increase in contractility. Talley, Meyer & McNay (1971) have shown that PEPI is a reliable index for estimation of changes in contractility when only small changes in preload and afterload are present as in this study. A shortening in PEPI was seen in all but two cases after dobutamine $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ as anticipated. At this dose level a very small decrease in diastolic pressure was seen, which would be accounted for by the slight decrease in the filling pressure expected after dobutamine (Beregovich *et al.*, 1975).

The two patients whose pulse pressure was unchanged by dobutamine showed little or no change of PEP. These cases had a high resting heart rate which increased after dobutamine or showed a marked increase in heart rate as the only response to the drug. They had either pre-existing congestive heart disease or signs of a large myocardial infarct with failure which were treated with diuretics and digitalis. In patients who had a high resting heart rate, dobutamine produced a small but significant rise in pulse pressure. In view of this, one could only expect a slight improvement in cardiac performance. The best response was seen in a relatively young patient with no previous heart disease and a myocardial infarct of moderate size. Dobutamine produced a marked increase in pulse pressure and shortening of PEPI. There was no increase in heart rate, possibly due to baroreceptor reflex depressor activity evoked by the increase in blood pressure. In this patient dobutamine had pure inotropic activity, as in the intact dog (Hinds & Hawthorne, 1975). In patients with little increase in pulse pressure after dobutamine there would be little baroreceptor reflex activity, and in these a chronotropic effect was seen as in vagotomized animals (Tuttle & Mills, 1975). In seven patients, only a slight decrease in diastolic pressure was seen as in patients with chronic heart disease and high peripheral resistance (Jewitt *et al.*, 1974). In one patient there was a marked drop in diastolic blood pressure which did not persist after cessation of infusion. A moderate increase in diastolic blood pressure was seen in two patients, who had hypertension and patho-anatomical changes in resistance vessels likely to make dilatation impossible. With higher doses of dobutamine the selectivity tended to decrease and so reduce the advantage of using the drug.

Continuous infusion of dobutamine $15 \mu\text{g kg}^{-1} \text{min}^{-1}$ counteracts the effect of an intravenous injection of metoprolol 15 milligrams. Since an increasing number of patients with angina pectoris, hypertension, arrhythmias will be treated routinely with β -adrenergic receptor blocking drugs, patients with acute myocardial infarction will often be under β -adrenoceptor blockade.

There will also be many β -adrenoceptor blocked patients who are in urgent need of surgery. Although many anaesthetists believe that β -adrenoceptor blocking drugs should be withdrawn some days before an operation (Viljoen, Estafanous & Kellner, 1972), this could be dangerous in patients who are well controlled on this therapy for angina pectoris, hypertension, and arrhythmias (Miller, Olson, Amsterdam & Mason, 1975).

On balance it seems best to continue chronic β -adrenoceptor blockade treatment during the early phase of acute myocardial infarction and during surgery, since in stressful situations, the ischaemic heart will need the protection of β -adrenoceptor blocking agents. However, in some patients, with poor heart function and risk of heart failure, β -adrenoceptor blockade may be hazardous, and for these a drug is required which will counteract the cardiodepressive effect of the β -adrenoceptor blocking agents. Isoproterenol has been most widely used when heart failure developed in patients on β -adrenoceptor blockade but

can be dangerous due to its arrhythmogenic activity. Dobutamine, with more marked inotropic than chronotropic activity and low arrhythmogenic potential, would be a most suitable agent.

In conclusion, the beneficial effects of dobutamine which were expected from studies on healthy animals subjected to local coronary obstruction are seen in subjects who have a recent cardiac infarct but whose cardiovascular system is otherwise not seriously impaired. The effects were not so clearly beneficial in patients who had severe left ventricular impairment.

Further, when dobutamine was given to patients under the influence of the β -adrenoceptor blocking agent, metoprolol, no arrhythmias or other unwanted effects were seen. Dobutamine may also be suitable to counteract the cardiodepressive effect of noncardio-selective β -adrenoceptor blockers such as propranolol and alprenolol but further studies have to be done. In patients under both β_1 and β_2 adrenoceptor blockade, dobutamine should increase peripheral vascular resistance since non-blocked vasoconstrictor α -receptors would be more activated than the partially blocked vasodilator β_2 -receptors. Our results suggest that dobutamine will be of value to counteract the cardiodepressive effects of β -adrenoceptor blocking drugs, especially cardioselective agents, in patients with acute myocardial infarction or undergoing surgery.

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